

Summary Basis for Regulatory Action

Date: 23-MAR-2011

From: Paula Ehrlich Agger MD MPH, Clinical Reviewer CBER/OVRR/DVRPA/CRB2

BLA/STN #: 125123/734

Applicant Name: Merck Sharp & Dohme Corp

Date of Submission: 25-MAY-2010

PDUFA Goal Date: 25-MAR-2011

Proprietary Name: ZOSTAVAX®

Additional Indication Sought Under this BLA Supplement: Prevention of herpes zoster (shingles) in individuals 50 years of age and older

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA, OVRR

Offices Signatory Action:

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Table 1 – Review Documents Used to Compile the SBRA

Review Category	Reviewer/Date of review
Clinical Review	Paula Ehrlich Agger MD MPH/22-MAR-2011
Statistical Review	Sang Ahnn PhD/ 21-JAN-2011
CMC Review	Shuang Tang PhD/08-FEB-2011
Bioresearch Monitoring	Solomon Yimam/08-FEB-2011
Labeling Review	Lisa Stockbridge PhD/19-OCT-2010

1. Introduction

ZOSTAVAX, a live attenuated varicella zoster virus (VZV) vaccine, is approved for prevention of herpes zoster (shingles) in individuals aged 60 years and older. The applicant submitted a supplemental Biologic License Application on 25-MAY-2010

seeking to extend the current indication to include subjects 50-59 years of age. In support of this application, the applicant submitted results from Protocol 022, A Phase 3, randomized, double blind, placebo controlled study of 22,439 subjects aged 50-59 who were randomized in a 1:1 ratio to receive either ZOSTAVAX or placebo. Subjects were followed for at least one year for the occurrence of herpes zoster. The statistical criterion for success was that the lower bound of vaccine efficacy against herpes zoster (VE_{HZ}) in the vaccine vs. the placebo group would be $> 25\%$.

2. Background

Herpes zoster (HZ) is the clinical reactivation of the varicella zoster virus. Following initial infection, the virus may remain latent in the sensory ganglia until reactivation occurs due to waning of cell mediated immunity, due to immunodeficiency or immunosenescence. Clinical HZ typically presents with a vesicular dermatomal rash accompanied by pain. The pain, which may be severe, can persist beyond rash healing. The incidence of HZ appears to rise sharply after age 45, with an approximate risk of 5 per 1000 per year for individuals aged 50-59. The incidence of zoster related complications, including post-herpetic neuralgia, also increases with age.

ZOSTAVAX clinical trial data in support of initial licensure was presented to the Vaccines and Related Biological Products Advisory Committee on 15-DEC-2005. The clinical efficacy trial, Protocol 004, also known as the Shingles Prevention Study (SPS), was conducted in subjects aged 60 and above. A smaller trial submitted in support of initial licensure, Protocol 009, which was designed to evaluate the safety of a higher potency dose of ZOSTAVAX, enrolled 185 individuals aged 50-59 of a total trial population of 698 enrolled subjects. Due to a lack of data of ZOSTAVAX efficacy in subjects aged 50 – 59, the committee voted unanimously against approval of ZOSTAVAX for use in subjects aged 50-59. The applicant submitted a new protocol (Protocol 015) on 14-DEC-2006, with plans to enroll ~ 4500 subjects aged 50-59, who would be randomized to receive ZOSTAVAX or placebo in a 2:1 ratio, and who would be followed for safety only. CBER responded that a randomized trial to evaluate safety, immunogenicity and efficacy in this population was recommended. Of special concern to CBER was the small benefit of zoster risk reduction expected through vaccination due to the low incidence of zoster in subjects aged 50-59, in relation to the risk of serious adverse events (SAEs) in general and cardiovascular SAEs in particular, both of which were found to be increased in ZOSTAVAX recipients as compared to placebo recipients in the Adverse Event Monitoring Substudy of the SPS. In response, the applicant submitted Protocol 022 on 13-JUL-2007, a randomized, double blind study of approximately 22,300 subjects aged 50-59 to evaluate the safety, immunogenicity and efficacy of ZOSTAVAX as compared to placebo.

3. Chemistry, Manufacturing and Controls

As this product was licensed at the time of this review, the CMC review was limited to the suitability and validation of the glycoprotein enzyme-linked immunosorbent assay (gpELISA) used to address a secondary hypothesis of the study; that ZOSTAVAX would elicit a higher VZV-specific antibody titer than placebo at 6 weeks post-vaccination. The statistical criterion for success of this hypothesis was that the lower bound of the 95%

confidence interval (CI) of the ratio of the geometric mean titers of ZOSTAVAX/placebo would be > 1.4. Serum from blood samples was assessed for VZV-specific antibody responses as measured by gpELISA on a pre-specified, randomized cohort of 10% of the total study population and on all subjects who develop suspected HZ.

The gpELISA has been used previously by Merck to measure the VZV antibody response in subjects vaccinated with ZOSTAVAX and VARIVAX. -----

----- (b)(4) -----

---. The product reviewer was concerned that since subjects aged 50 – 59 may have stronger immunoresponses to vaccination with ZOSTAVAX than subjects aged 60 and over or aged 1 – 12 that had been vaccinated with ZOSTAVAX or VARIVAX, respectively, and that the responses therefore might be out of the validated range of the assay. However, the VZV antibody responses (GMT and GMFR) induced by ZOSTAVAX in 50-59 year old subjects was not significantly different from those in subjects aged 60 years and older. Therefore, the conclusion was made that the VZV specific gpELISA was suitable for use in the 50-59 year old age group.

The CMC reviewer also noted that the validation of the gpELISA was previously completed by Merck in their own laboratories, but not by PPD Vaccines and Biologics, LLC (PPD), where the tests were performed for this study. In a response to this concern, the applicant responded that on 05-JAN-2009, PPD acquired the entire Merck testing unit without changing the facility, SOP and personnel, and for that reason, no revalidation for the gpELISA was necessary. This was felt to be acceptable.

4. Nonclinical Pharmacology/Toxicology

There was no nonclinical pharmacology or toxicology review for this efficacy supplement.

5. Clinical Pharmacology

There was no clinical pharmacology review for this efficacy supplement.

6. Statistical

Upon completion of enrollment, the applicant noted in a communication with CBER that the study enrolled 22,444 subjects from 29-OCT-2007 to 17-OCT-2008 (10.5% over initial targeted enrollment) with approximately 20% of subjects enrolled in the final 6 weeks of the enrollment period. The applicant justified the enrollment of an additional 2000 subjects by stating that both expected enrollment in the last 6 months of the trial as well as slow accrual of HZ cases warranted the increase. The applicant also noted that in the SPS, vaccine efficacy was noted to be highest during the first 6 months post-vaccination, leveling off and remaining stable for the remainder of year 1 and through year 4. In response, CBER recommended that all subjects have one year of follow-up, and the applicant concurred.

In the final statistical review, the statistician noted that all datasets were in the appropriate format (.xpt files) and the define file (define.xml) properly explained variables in each dataset. The efficacy tables in the clinical study report (11-1 through 11-4, 11-10 and 11-16) were verified with concurrence between the statistical reviewer's and the applicant's efficacy analyses. The statistical reviewer stated that in the ITT population, the estimated vaccine efficacy (VE) was 69.8% with a 2 sided confidence interval (CI) of (54.7%, 79.8%) which met the pre-specified success criterion for this endpoint. Post-hoc subgroup efficacy results by gender indicated that VE was higher in females [VE = 73.8% with a 95 % CI of (57.4, 83.9)] than males [VE = 55.0% with a 95% CI of (6.6, 78.3)]. Subgroup analyses by race and age were not performed, as ~ 94% of the subjects were white and all subjects were aged 50-59.

7. Clinical

One randomized, double-blind, placebo-controlled trial in which all the subjects (except one 70 year old mistakenly enrolled) were 50-59 years of age was submitted to the supplemental Biologic License Application (sBLA). The trial examined safety, immunogenicity and efficacy. In assessing the overall risk/benefit ratio for administering ZOSTAVAX to subjects aged 50-59, the study data from Protocol 022 was of primary importance. In addition, information from the pivotal trial for licensure (Protocol 004), post-marketing study results, as well as the literature regarding incidence of HZ and HZ complications were considered.

Efficacy

The applicant submitted Protocol 022 in support of the expansion of the indication to include 50-59 year olds. In this protocol, 22,439 individuals aged 50-59 were randomized to receive either one dose of ZOSTAVAX or placebo in a 1:1 ratio. Subjects were followed for the occurrence of HZ for a minimum of 1 year, with contacts made monthly by phone or internet. The primary hypothesis of the study was that vaccination with ZOSTAVAX would reduce the incidence of HZ compared with placebo in subjects 50-59 years of age, with the statistical criterion for success requiring that the lower bound of the 95% CI for vaccine efficacy against HZ would be > 25. The efficacy analysis was based on the intent-to-treat approach.

The point estimate of vaccine efficacy, defined as the relative reduction in the incidence rate of HZ in the ZOSTAVAX group compared with that of the placebo group, was 69.8% (95% CI: 54.1%, 80.6%). This was based on the occurrence of 30 confirmed cases of HZ in the ZOSTAVAX group (out of 109 suspected cases) and 99 confirmed cases of HZ in the placebo group (out of 168 suspected). Of the 277 suspected cases of HZ, 80.5% had final determination (as a case, or not a case, of HZ) by polymerase chain reaction results of lesion samples, while 19.5% had final determination by case adjudication.

Durability of vaccine efficacy was analyzed in 6 month intervals. Since the numbers of subjects followed declined as the years progressed, the estimate by year is less precise than the overall estimate. Vaccine efficacy appeared to remain stable from years 0 to 1.5. Beyond 1.5 years, fewer subjects had follow-up, thus too few HZ cases occurred to

meaningfully interpret VE beyond 1.5 years from the data in this age group. Durability of vaccine efficacy in the SPS was demonstrated through year 4 post-vaccination, and it is expected that durability of vaccine effect would be similar in subjects aged 50-59.

Safety

The safety population included all vaccinated subjects who had any safety follow-up. The safety database consisted of over 99% of all vaccinated subjects (99.2% of ZOSTAVAX and 99.1% of placebo recipients). Approximately 97% of subjects in both treatment groups completed the 6 month safety follow-up.

The primary safety endpoint was the incidence of serious adverse events observed during the 42 day primary safety follow-up period in each vaccination group. There was no hypothesis testing or statistical criterion for success related to safety.

During the primary safety period (Days 1 – 42) there was 1 death in the ZOSTAVAX group and 2 deaths in the placebo group. The ZOSTAVAX recipient was a 57 year old white male with a history of hypertension, alcohol abuse, cirrhosis of the liver and chronic obstructive pulmonary disease who fell and died at home after several days of alcohol consumption. The cause of death was listed as hypertensive cardiomyopathy and liver cirrhosis and a ruptured bladder due to the fall were noted on the autopsy report. None of the 3 deaths in the Day 1 – 42 safety period were assessed by the investigator as being related to study product.

There were a total of 48 deaths recorded in the entire study, 18 in the ZOSTAVAX group and 30 in the placebo group. None were attributed by the investigator as due to study product. These deaths were reviewed, and while in most cases the causes and manners of death were typical of what might be expected of this age group and consistent with the subjects' past medical history, in some cases there were scant details of the causes of death. However, there were more deaths in the placebo than in the ZOSTAVAX group, and in general the listed causes were comparable between treatment groups, and low as compared to the overall U.S. death rate of subjects aged 50-59.

There were 69 subjects in the ZOSTAVAX group (0.6% of subjects) and 61 subjects in the placebo group (0.5% of subjects) experiencing SAEs in the primary safety period from Days 1- 42. During the Day 1 – 182 reporting period, there were 235 subjects (2.1%) in the ZOSTAVAX group and 213 subjects (1.9%) in the placebo group reporting SAEs. The number of subjects and types of SAEs reported were comparable between treatment groups.

There was one vaccine related SAE reported in a 52 year old white female who experienced anaphylaxis shortly after ZOSTAVAX vaccination. She was treated emergently and had a full recovery.

There was a clinically significant difference between the numbers of subjects experiencing the solicited adverse events (AEs) of injection site pain, swelling and erythema collected on Days 1 – 5 post-vaccination between treatment groups, with 63.6%

of ZOSTAVAX recipients and 14.0% of placebo recipients reporting injection site AEs on Days 1 – 5. However, most injection site AEs were mild and resolved without sequelae.

There was a slight difference in the number of subjects reporting unsolicited AEs in the ZOSTAVAX group (35.4%) vs. the placebo group (33.5%), which appeared to be due to the specific AE of headache.

The Clinical Evaluation Committee, which was charged with reviewing each suspected case of HZ, determined that no HZ complications occurred in confirmed cases during the study. No cases of post herpetic neuralgia were recorded.

9. Other Relevant Regulatory Issues

-----Information Withheld Per the Privacy Act-----

-----	-----	-----	-----
-----	-----	-----	-----
-----	-----	-----	-----
-----	-----	-----	-----

10. Labeling

The applicant submitted changes to the Prescribing Information (PI) and Patient Package insert (PPI) incorporating data from Protocol 022. Both documents were evaluated by the review team in conjunction with reviewers from the Advertising and Promotional Labeling Branch (APLB). Clarifications, revisions and additions to the PI were made, and were agreed upon by the review team, APLB and Merck, Sharp and Dohme Corp. A significant development was the change of pregnancy category from Category C to Pregnancy Category: Contraindicated. This change was made as assigning an alphabetized pregnancy category as per 21 CFR 201.57 was not possible given both the lack of specific data with this live virus vaccine corresponding to the information in the categories and the mandatory labeling language for the categories. After discussions with CBER, Merck submitted a waiver of the alphabetized pregnancy categories in Amendment #7 on 09-MAR-2011, which was granted. In addition, the language regarding concomitant administration of ZOSTAVAX and PNEUMOVAX23 was revised, as clinical relevance of the results of a randomized trial in which reduced immune response as measured by gpELISA in subjects administered the vaccine concomitantly as compared to those who did not receive it concomitantly is not known. The language in the Highlights section (Drug Interactions) and Section 7.1 (Concomitant Administration with Other Vaccines) of the PI was revised to include information about the concomitant administration clinical study as well as to advise clinicians to consider non-concomitant administration of the vaccines. The PPI was also updated to reflect this change.

11. Postmarketing

The following Post Marketing Commitment has been agreed upon:

1. To conduct a large scale observational study of US subjects aged 50 to 59 years of age vaccinated with ZOSTAVAX® to assess the long-term effectiveness of the vaccine and better characterize the duration of protection against herpes zoster (HZ).
 - Concept Protocol Submission Date: March 14, 2011
 - Final Protocol Submission Date: December 31, 2011
 - Study Initiation Date: June 2012
 - Interim Study Report Submission Date: The first interim study report is anticipated to be submitted in December 2016 or approximately 5 years after ZOSTAVAX is recommended by the ACIP (assumed to be in June 2011). A second interim study report is anticipated to be submitted in December 2020.
 - Study/Trial Completion Date: Either follow-up to June 2023 or follow-up of approximately 5000 subjects 50-59 years of age for 10 years, whichever comes first. The duration of the study will be dependent upon several factors including the retention rate at the study institution and uptake of ZOSTAVAX. Vaccine uptake is influenced by multiple factors including, but not limited to, ACIP recommendations for 50-59 years olds, vaccine supply availability, and healthcare provider and patient attitudes and decisions.
 - Final Report Submission Date: December 2024

11. Recommendation and Risk/Benefit Assessment

- a) Recommended Regulatory Action – Approval of this BLA Supplement for ZOSTAVAX for prevention of herpes zoster (shingles) in individuals 50 years of age and older is recommended.
- b) Risk/Benefit Assessment – Although ZOSTAVAX has demonstrated efficacy and has an acceptable safety profile in the 50-59 year old age group, the risks of vaccine administration must be balanced with the benefit of preventing clinical events of low incidence in this population and with the consideration that natural reactivation may confer life long protection against future recurrences of HZ.
- c) Recommendation for Risk Management Postmarketing Activities – None recommended.
- d) Recommendation for Postmarketing Activities – To conduct a large scale observational study of U.S. subjects aged 50 to 59 years vaccinated with ZOSTAVAX to assess the long-term effectiveness of the vaccine and better characterize the duration of protection against herpes zoster.